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ACUTE TOXICITY OF 3,3-DIETHYNLDIPHENOL SULFONE, AN ACETYLENE TERMINATED SULFONE

J. R. HORTON
C. L. GAWORSKI
J. D. MacEWEN
E. H. VERNOT

UNIVERSITY OF CALIFORNIA, IRVINE
P. O. BOX 3067, OVERLOOK BRANCH
DAYTON, OHIO 45431

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AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OHIO 45433

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

ROGER C. INMAN, Colonel, USAF, BSC
Chief
Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)* Acetylene terminated sulfone or 3,3-diethynldiphenol sulfone was subjected to a battery of acute animal toxicity studies for estimation of its potential health hazards to production or material handling workers. These studies included acute oral, acute dermal, eye irritation, skin irritation and skin sensitization testing. Inhalation studies could not be performed because the tacky nature of the finely ground material prevented generation of an aerosol. The fine

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particles rapidly clumped together forming larger and larger irregular shaped masses up to several inches in size.

All of the acute toxicity tests conducted were negative at the levels tested in the animal models used, and it is probable that this material can be handled without harmful acute effects by workers using standard hygienic precautions.

PREFACE

This is one of a series of technical reports describing the results of the experimental laboratory program being conducted in the Toxic Hazards Research Unit (THRU). This document constitutes a Final Report on the Acute Toxicity of 3,3-Diethynldiphenol Sulfone, an Acetylene Terminated Sulfone. The research covered in this report began in November 16, 1981 and was completed in January 29, 1982 and was performed under Air Force Contract No. F33615-80-C-0512, work unit 63020115. M. K. Pinkerton served as the technical contract monitor for the Air Force Aerospace Medical Research Laboratory.

J. D. MacEwen, Ph.D., served as the Laboratory Director for the THRU of the University of California, Irvine and as co-principal investigator with T. T. Crocker, M.D., Professor and Chairman, Department of Community and Environmental Medicine.

TABLE OF CONTENTS

	Page
INTRODUCTION	3
MATERIALS	3
Animals	4
METHODS	4
Oral Toxicity	4
Dermal Toxicity	4
Primary Eye Irritation - Rabbit	5
Primary Skin Irritation - Rabbit	5
Sensitization - Guinea Pig	6
RESULTS	7
DISCUSSION	10
REFERENCES	11

LIST OF TABLES

Table		Page
1	Acute Oral Toxicity of ATS for Rats	7
2	Acute Oral Toxicity Body Weight Data for Sprague Dawley Rats Treated with ATS Suspended in Vegetable Shortening	8
3	Acute Dermal Toxicity of ATS for Rabbits	9
4	Acute Dermal Toxicity Body Weight Data for Rabbits Treated with ATS	9
5	Effect of ATS on Rabbit Eyes	9
6	Effect of Dermal Application of ATS on Rabbits' Skin	10
7	Skin Sensitization Potential of ATS to Guinea Pigs	10

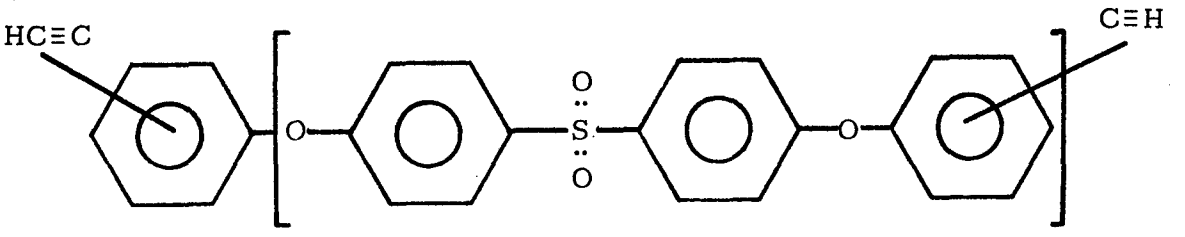
INTRODUCTION

The United States Air Force has conducted a continuing program for the development of better moisture resistant, high temperature resins for use as composite matrices. One compound, 3,3-diethynldiphenol sulfone, developed by the Materials Laboratory at Wright-Patterson Air Force Base, Ohio has shown considerable promise for this purpose. This material, also known as ATS (acetylene terminated sulfone) is a mixture of approximately 80% monomer and 20% other oligomers.

Health hazards associated with the manufacture and handling of ATS have not been defined nor were any human or animal exposure data available for estimation of its toxicity. To provide this information the Toxic Hazards Research Unit of the University of California, Irvine was requested to conduct a comprehensive acute toxicity study.

MATERIALS

ATS is a yellowish resin with a sticky consistency and a strong acrid odor. The odor is probably due to some low level contaminant containing bromine which is used in the manufacturing processes. The structure of ATS is shown below:



The probable isomer composition is as follows:

n = 1	meta,meta	72%		
	meta,para	7%	n = 1	80%
	para,para	1%		
n = 2	meta,meta,meta	14%	n = 2	16%
	meta,meta,para	2%		
n = 3	meta,meta,meta		n = 3	3%
Other oligomer isomers		$\leq$ 1%		

Impurities other than the bromine containing material that provides the strong odor in the ATS samples received for toxicity studies were identified by the Materials Laboratory as 6 ppm copper, 25 ppm palladium, 1.5% methylbenzene, and 0.75% diethynylbenzene.

ANIMALS

Male and female New Zealand white rabbits were obtained from Willoughby's Rabbitry, Sabina, Ohio. Male and female Sprague-Dawley derived rats were purchased from Charles River Breeding Laboratories, Wilmington, Mass. Female, Hartley derived guinea pigs were obtained from Murphy Breeding Laboratories, Plainfield, Ohio.

METHODS

Oral Toxicity

ATS was administered as a finely ground powder suspended in a vehicle. Considerable difficulty was encountered in finding a suitable vehicle for preparing the ATS suspensions. ATS rapidly agglutinated into particle sizes that were too large to be forced through an oral dosing needle when suspended in corn oil, peanut oil, propylene glycol, polyethylene glycol, petrolatum, or agar. The ATS was not sufficiently soluble in acetone, ethanol, or DMSO to utilize them as vehicles for intubation.

We determined empirically that a 10% wt/volume mixture of finely ground ATS in vegetable shortening could be extruded through a dosing needle with slight difficulty. Therefore, groups consisting of 5 male and 5 female rats were orally administered this mixture at 2% of their body weight. Dosing at 2% of body weight resulted in a uniform dose of 2000 mg/kg for all treated rats. The animals had been fasted overnight prior to the dosing. After dosing the animals were observed for mortality and signs of toxicity for a 14-day postadministration period.

Dermal Toxicity

Male albino New Zealand rabbits were used to determine the dermal toxicity of ATS. The hair on the backs of the rabbits and the sides halfway to the abdomen was clipped from the top of the shoulders to the top of the hind leg area 24 hours prior to dosing. Two grams/kg body weight of finely ground ATS was applied undiluted to the backs of the rabbits and was divided as equally as possible between the two sides. The dose was held in place by

applying 8 ply gauze patches over the material on each side of the back. A patch of pure latex rubber dental dam was applied over the entire clipped back area and elastic adhesive tape was used to wrap the entire midsection of the rabbit to hold the material in place. Specially designed rabbit restraining harnesses were fitted to each rabbit at the time of dosing and kept in place during the entire dosing period. These harnesses prevented excessive movement of the rabbits and prevented them from chewing or removing the tape. The harnesses did, however, allow the rabbits access to food and water, ad libitum

All doses of ATS were kept in contact with the rabbit's skin for 24 hours. After 24 hours the harnesses were taken off and the tape, latex and gauze removed. The rabbits were maintained in individual cages postexposure and observed for mortality or other signs of toxicity during the 14 days immediately following exposure.

Primary Eye Irritation - Rabbit

One-tenth gram of finely ground ATS was applied to one eye of each of nine albino rabbits. The opposite eye was untreated and served as a control. The treated eyes of six rabbits remained unwashed. The treated eyes of the remaining three rabbits were then irrigated for no less than one minute with lukewarm water starting no sooner than 20-30 seconds after instillation of the ATS. Examinations for gross signs of eye irritation were made at 24, 48, and 72 hours postapplication. Scoring of irritative effects was performed according to the method of Draize (1959) in which corneal, iris, and conjunctival effects are scored separately. In this scoring system, injuries to the cornea and iris may represent as much as 80% of the total score. Cornea and iris scores are numerically weighted because of the essential role of these tissues in vision.

Primary Skin Irritation - Rabbit

A patch-test method was utilized to determine the ability of ATS to cause primary skin irritation of intact or abraded skin of albino rabbits.

Six rabbits were clipped of all possible hair on the back and flanks. The clipping was done 24 hours prior to exposure to allow for recovery of the skin from any abrasion. One of the two areas on the back was abraded by making minor incisions through the stratum corneum, not sufficiently deep to disturb the dermis or to produce bleeding. A syringe needle was used to make incisions in a cross hatch pattern.

A 0.5 gram sample of the finely ground test material was applied in equal 0.25 gram amounts to the designated patch areas and covered by a 1-inch square of surgical gauze two single layers thick. The gauze patches were held in place with strips of elastoplast tape and the entire area covered with a rubber dental dam strip secured with more elastoplast tape. These patches remained in place on the rabbits for 24 hours. During that time, the rabbits were fitted with leather restraining collars. These collars prevented disturbance of the patch area, while allowing the rabbits freedom of movement and access to food and water during the test period. After 24 hours, the wrap and patches were carefully removed, and the test areas evaluated for irritation using the Draize (1959) table as a reference standard. Examinations were made at 48 and 72 hours to determine irritation effects.

Sensitization - Guinea Pigs

A preliminary screening test was conducted with 3 guinea pigs to determine that the dosage of ATS used for sensitization tests would not produce primary skin irritation over a 24 hour period. When the ATS was found non-irritating to the flanks of the guinea pig tested, ten new female albino guinea pigs were selected for the skin sensitization study. The animals used in this study were Hartley strain and were 6 to 8 weeks old when the treatments were initiated.

Using the method of Maguire (1973), an area on the back of each animal directly above the forelegs was clipped with electric clippers and residual hair was removed with a commercial depilatory on the morning of the first insult exposure. One ml of a 10% wt/volume suspension of ATS in peanut oil was applied to this area on a 1/2 x 1/2 inch cotton gauze square, covered with dental dam, and held in place with adhesive tape. Because the ATS particles in suspension agglutinated with standing it was necessary to prepare fresh material for each application. The first insult patch remained in place for two days, was then removed, and a second application of 0.1 gram made. Two days later, the second patch was removed, 0.2 ml of a 50% aqueous dilution of Freund's* adjuvant per animal was injected intradermally, using 2 or 3 points of injection adjacent to the insult site, then a new patch of 0.1 g of the test

* Bacto Adjuvant Complete, Freund, Difco Laboratories, Detroit, Michigan.

material was applied. The patch was removed and another new patch of 0.1 gram of the test material applied 3 days later. The last patch was removed 2 days later, and the animals were allowed to rest for two weeks. Each time the insult patches were removed, the condition of the skin at the application site was evaluated and recorded. When the last patch was removed, the toes of the hind feet of each animal were taped to prevent the animal from scratching the irritated area.

After the two-week rest period, both flanks of the animals were clipped and challenged on one side with ATS (0.1 gm in peanut oil) and straight peanut oil vehicle was applied on the other flank. The challenge applications were not occluded. The skin response at these sites was recorded at 24 and 48 hours post application. Any animal showing measurable erythema and/or edema at the test solution challenge site was rated as a positive responder.

The sensitization test was duplicated using ATS dissolved in acetone for comparative purposes. Although ATS was not sufficiently soluble in acetone to prepare concentrations necessary for oral dosing it was suitable for this purpose.

RESULTS

There was no mortality nor were there signs of toxicity when male and female rats were orally administered a 2000 mg/kg dose of finely ground ATS suspended in vegetable shortening. Male and female rats used as vehicle controls were unaffected by the administration of straight vegetable shortening at 2% of their body weight. The mortality data are summarized in Table 1, and individual body weight data are given in Table 2.

TABLE 1. ACUTE ORAL TOXICITY OF ATS FOR RATS

Sex	No of Animal	Dose Level (mg/kg)	Dose Vol % of Body Wt	No of Animals Dead/Symptoms/Exposed
male	5	2000	2%	0/0/5
female	5	2000	2%	0/0/5
male	5	--	2%	0/0/5
female	5	--	2%	0/0/5

TABLE 2. ACUTE ORAL TOXICITY BODY WEIGHT DATA FOR SPRAGUE DAWLEY RATS TREATED WITH ATS SUSPENDED IN VEGETABLE SHORTENING

Animal Number	Sex	ATS Dose (mg/kg)	Dose Volume (%)	Body Weight (grams) Day 0	Day 7	Day 14
12	male	0	2%	307	377	417
13	male	0	2%	302	358	390
14	male	0	2%	338	410	450
15	male	0	2%	310	360	396
16	male	0	2%	315	375	395
mean				314	376	409
6	male	2000	2%	330	395	436
7	male	2000	2%	340	400	439
9	male	2000	2%	295	336	372
10	male	2000	2%	335	390	427
11	male	2000	2%	320	375	403
mean				324	379	415
6	female	0	2%	208	238	246
7	female	0	2%	235	270	276
8	female	0	2%	242	266	280
9	female	0	2%	208	229	275
10	female	0	2%	225	263	274
mean				223	253	270
12	female	2000	2%	225	250	264
13	female	2000	2%	240	268	288
14	female	2000	2%	231	262	267
15	female	2000	2%	203	260	277
16	female	2000	2%	204	230	244
mean				220	254	268

Dermal exposures of male rabbits to a 2000 mg/kg dose for 24 hours did not demonstrate any signs of toxicity or delayed deaths over a 14 day observation period. The results of this test are shown in Table 3. Body weights for individual animals are listed in Table 4.

TABLE 3. ACUTE DERMAL TOXICITY OF ATS TO RABBITS

Sex	No of Animals	Dose (mg/kg)	Exp Time (hrs)	Vehicle	No of Animals Dead/Symptoms/Exposed
male	3	2000	24	None	0/0/3

TABLE 4. ACUTE DERMAL TOXICITY
BODY WEIGHT DATA FOR RABBITS TREATED WITH NEAT ATS

Animal Number	Sex	Dose (mg/kg)	Exposure Time (hr)	Body Wt (kg) Day 0	Day 14
A18	male	2000	24	1.7	2.2
A16	male	2000	24	1.9	2.4
A20	male	2000	24	1.7	2.2

The administration of finely ground ATS into the eyes and on the skin of rabbits resulted in no primary irritation. The negative results of these primary irritation studies are summarized in Tables 5 and 6.

TABLE 5. EFFECT OF ATS ON RABBIT EYES

Animal No	Eye Washed	Numerical Score 24 hr.	48 hr.	72 hr.
K32	No	0	0	0
K26	No	0	0	0
K30	No	0	0	0
K28	No	0	0	0
K22	No	0	0	0
K24	No	0	0	0
D75	Yes	0	0	0
K34	Yes	0	0	0
K36	Yes	0	0	0
Total		0	0	0

TABLE 6. SKIN IRRITATION OF ATS

	Scoring			
	24 hrs. Post Appl.		48 hrs. Post Appl.	
Animal Number	Erthyma Intact/Abraded	Edema Intact/Abraded	Erythema Intact/Abraded	Edema Intact/Abraded
K32	0/0	0/0	0/0	0/0
K26	0/0	0/0	0/0	0/0
K30	0/0	0/0	0/0	0/0
K28	0/0	0/0	0/0	0/0
K22	0/0	0/0	0/0	0/0
K24	0/0	0/0	0/0	0/0
Total	0	0	0	0

The sensitization potential of ATS for guinea pigs was found to be negative when tested with either peanut oil or acetone as the treatment vehicle. The results are listed in Table 7.

TABLE 7. SKIN SENSITIZATION POTENTIAL OF ATS TO GUINEA PIGS

			Mean* Challenge Reaction Score			
			24 hrs. Post		48 hrs. Post	
No of Animals	Sex	Vehicle	ATS Site	Control Site	ATS Site	Control Site
10	female	peanut oil	0	0	0.1	0
10	female	acetone	0	0	0	0

* Challenge reactions were evaluated on a scale of 0-4.

DISCUSSION

Acetylene terminated sulfone or 3,3-diethynldiphenol sulfone was subjected to a battery of acute animal toxicity studies for estimation of its potential health hazards to production or material handling workers. Inhalation studies could not be performed because the tacky nature of the finely ground material prevented generation of an aerosol. The fine particles rapidly

clumped together forming larger and larger irregular shaped masses up to several inches in size.

All of the acute toxicity tests conducted were negative at the levels tested in the animal models used, and it is probable that this material can be handled without harmful acute effects by workers using standard hygienic precautions.

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